Kidney International, Vol. 37 (1990), pp. 110–115

Epidemic hypotension in a dialysis center caused by sodium azide

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Epidemic hypotension in a dialysis center caused by sodium azide. The water used for dialysate (dialysis fluid) in hemodialysis centers is produced by water treatment systems (WTS), which require careful and frequent monitoring. On November 3, 1988, nine patients receiving hemodialysis treatments at a single dialysis center suddenly developed hypotension within 30 minutes of onset of dialysis. Eight patients exhibited symptoms and two experienced syncopal episodes; there were no deaths. The incidence of dialysis-associated hypotension occurring within 30 minutes after dialysis onset for these patients was significantly higher during outbreak treatments than during preoutbreak (September 1 through November 2, 1988) treatments, (9 of 9 vs. 0 of 238, $P < 0.00001$, Fisher's *t*-test). Sodium azide, a potent hypotensive agent, was identified as the probable contaminant within the WTS of the dialysis center at the time of the outbreak because: 1) it was mixed with glycerine as the preservative solution of each of the four ultrafilters that were put on-line in the WTS without rinsing, 12 hours before the outbreak; and 2) high levels of total organic carbons were detected from dialysis water collected at point-of-use sites at the time of the outbreak, suggesting contamination of the WTS with the sodium azide-glycerine preservative solution. To prevent similar occurrences, we recommend that ultrafilters (and other components of the WTS) be rinsed free of potentially toxic chemicals prior to use. Dialysis center personnel need to be aware of the potential affects that each modification or disinfection of the WTS may have upon the product water used to prepare dialysate for patient treatments.

The Association for the Advancement of Medical Instrumentation (AAMI) recommends that water used for the production of dialysate (dialysis fluid) should be treated to remove organic and inorganic substances and microbial contaminants [1]. Certain chemicals in water are harmless when ingested but toxic to hemodialysis patients who can be exposed to 150 liters of water per treatment. Adverse affects have occurred among patients exposed to dialysis water containing high concentrations of aluminum (dialysis dementia) [2–3], zinc [4], copper [5], fluorides [6], calcium [7], sodium [8], chloramines [9, 10], and hydrogen peroxide (Centers for Disease Control, unpublished data).

We report an outbreak of epidemic hypotension among a group of patients during hemodialysis treatments in a dialysis unit in New York State during November 1988, in which the dialysate was inadvertently contaminated with sodium azide.

Received for publication May 26, 1989
and in revised form August 10, 1989
Accepted for publication August 14, 1989

Background

The dialysis unit has been in operation at its present location since January 1982. The unit has 19 dialysis stations. At the time of the investigation 71 adults were receiving chronic hemodialysis with Lundia IC plate dialyzers[1] (Gambro Lundia, AB, Sweden) and Gambro AK-10 dialysis monitors (Gambro Lundia, AB, Sweden). The acetate or bicarbonate concentrate was proportioned automatically at each individual monitor. Dialyzers were not reused.

Water treatment system

The water treatment system (WTS) at the dialysis unit consisted of: 1) pretreatment; 2) the ultrafilter loop; 3) the reverse osmosis (RO) unit; 4) the distribution loop which included 19 dialysis stations and a 600 gallon holding tank (Fig. 1).

Community supplied water was distributed through the hot and cold water lines at the dialysis center, mixed to approximately 26°C, and flowed sequentially through a sand filter, a carbon filter, and a 10-micron cotton sediment filter.

The water next passed through four hollow-fiber ultrafilters aligned in parallel, and into a ultrafilter water holding tank. A pump maintained adequate operating pressure within the ultrafilter loop to permit continuous recirculation of ultrafilter treated water from the ultrafilter holding tank through the ultrafilter recirculation loop. Upon demand, water flowed from the ultrafilter distribution loop to the RO unit. To reduce accumulated debris, back-flushing of the ultrafilters occurred automatically at 1830 and 0100 hours.

The RO unit includes a 1-micron prefilter, a pump to maintain the operating pressure required to operate the RO unit, and two RO cartridges, each containing two RO membrane nodules. The RO membranes are set up in a single pass 1:1 serial array. The rejected water (effluent) was run-off to a drain, while the permeate (RO product water) passed through to the 600-gallon

[1] Use of trade names and commercial sources is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.

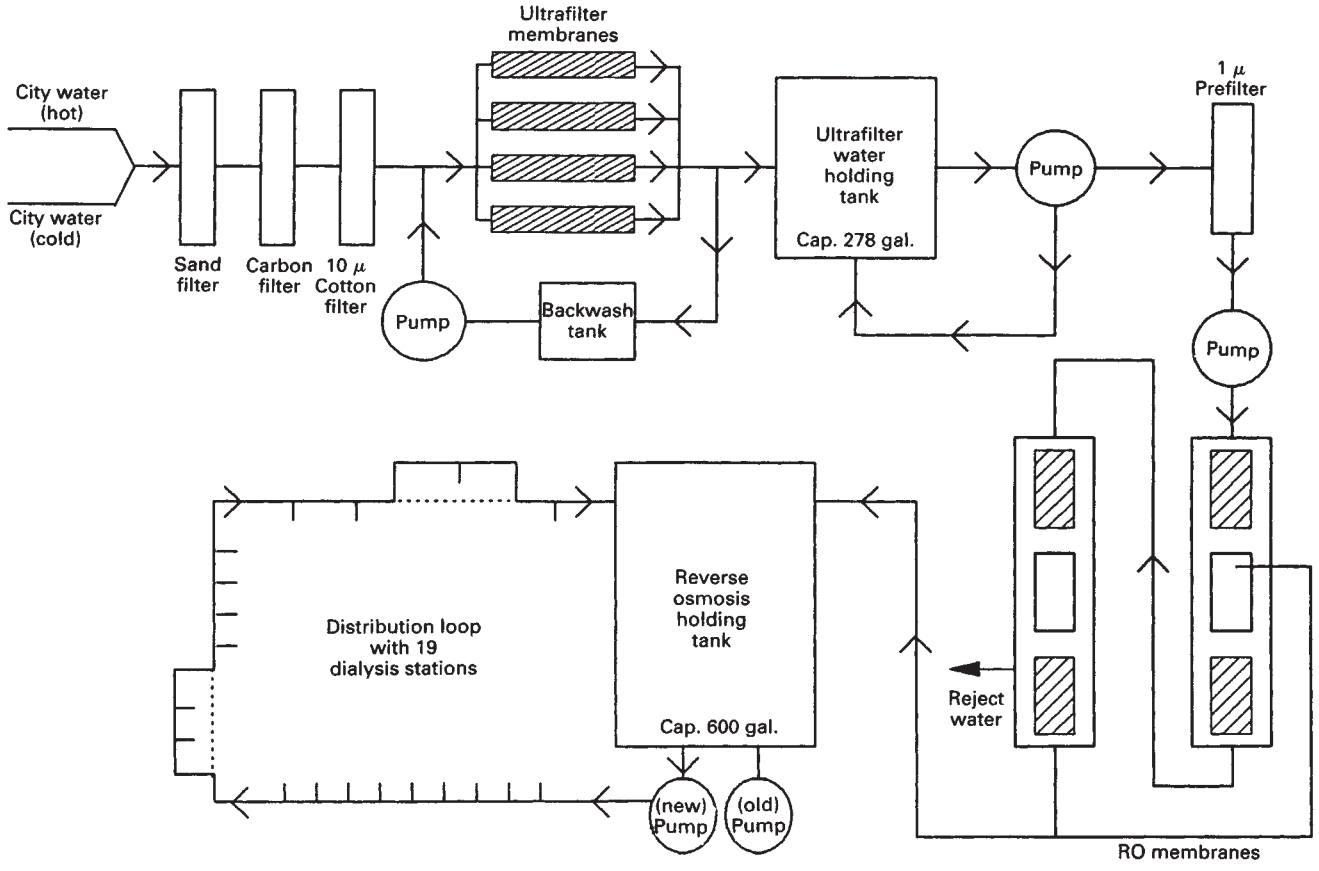

Fig. 1. *The water treatment system of a New York dialysis center, November 1988.*

capacity RO holding tank. The RO unit was activated to fill the RO holding tank upon demand.

A pump, located adjacent to the RO holding tank, continuously recirculated RO product water from the tank to the 19 dialysis stations. If the dialysis stations were not in use, the water returned via approximately 400 feet of piping to the RO holding tank.

Modification of the WTS on November 2, 1988

Between 1800 and 2000 hours on November 2, 1988, workmen completed three modifications of the WTS at the dialysis unit. First, an auxiliary electrical system was installed to provide a back-up source of power to the pumps within the WTS. The integrity of the WTS was not violated during this process. Second, an additional (5 hp) pump was installed adjacent to the RO storage tank to provide an increased rate of flow of product water within the distribution loop for the anticipated expansion of dialysis stations. New plumbing connecting the RO storage tank, the new pump, and the distribution loop was fitted; this process required the RO storage tank water to be drained to a level of approximately 40 gallons. Third, the four ultrafilters on-line (GM80-HF53 Romicon, Inc., Woburn, Massachusetts, USA) were replaced with four new identical ultrafilters per routine maintenance protocol. Each ultrafilter is composed of 2940 non-cellulosic synthetic polymer hollow fibers 43 in length and 0.1 micron thick, with an approximate surface area of 53 sq ft. Prior to shipping, the hollow fibers are treated with a preservative (0.25% sodium azide and 25% glycerine solution). The manufacturer recommends a rinse procedure to flush out both the ultrafilter hardware and cartridge before installation. However, no warning label or instructions were included with the shipment of the new ultrafilters, and they were not rinsed before being put on-line in the WTS.

At 2000 hours on November 2, 1988 the WTS was put back on-line. Dialysis treatments resumed at 0610 hours on November 3, 1988.

The incident of epidemic hypotension among patients receiving dialysis treatments

Between 0610 and 0715 hours on November 3, 1988, nine patients began their regularly scheduled dialysis treatments. By 0730 hours, nursing personnel identified significant signs and symptoms of hypotension among several patients; all dialysis treatments were stopped by 0805 hours. Contamination of the water within the WTS was suspected as the cause for these adverse reactions because of the modifications of the WTS performed during the previous evening. Water at point-of-use stations was checked for chloramines and chlorine and tested negative. Additional fluid specimens were collected from a single point-of-use station, the distribution loop, the RO storage tank, and from the faucet. Serum samples were collected from each patient at 0830 hours along with samples from the dialyzers used during their treatments. The WTS was bypassed using

tubing to connect the dialysis machines to tap water faucets, and hemodialysis treatments resumed at 1100 hours. Subsequently, two mixed-bed deionization tanks were installed within the WTS on November 5 at 1700 hours, bypassing both the ultrafilters and the RO unit, providing deionized water to the point-of-use distribution loop.

Epidemiologic investigation

During the epidemic period, defined as the period of time between 0610 and 0815 on November 3, several patients receiving hemodialysis experienced sudden onset of unexplained symptomatic hypotension. We wanted to answer the following questions: 1) Was the incidence of hypotension among these particular patients undergoing chronic hemodialysis unusual? and 2) Did these patients experience hypotension as a result of their dialysis treatments with water contaminated within the WTS?

Methods

A case was defined as any patient who had undergone dialysis at the dialysis unit between 0610 and 0815 hours on November 3, 1988, who had a fall in systolic blood pressure >50 mm Hg from the blood pressure measurement obtained immediately before treatment to a level <90 mm Hg, or a fall in systolic blood pressure ≥80 mm Hg from the blood pressure measurement obtained immediately prior to treatment to a level ≤100 mm Hg, within 30 minutes after onset of hemodialysis.

We defined hypotension during hemodialysis as a fall in systolic blood pressure >30 mm Hg from the blood pressure measurement obtained immediately before treatment to a level <90 mm Hg at any time after onset of dialysis.

We reviewed the records of the case-patients for dialysis treatments occurring immediately prior to, during, and after the outbreak exposure treatment on November 3. Data collected included: patient age, race, sex; cause of end-stage renal disease; total years of hemodialysis; total number of hemodialysis treatments at the dialysis unit; dialyzer type; which dialysis machine; date, onset and duration of hemodialysis treatments; pre-, intra-, and postdialysis vital signs (including onset of lowest recorded intradialytic blood pressure); symptoms of nausea and emesis, headache, cramps, subjective chills, or rigors; and receipt of intradialytic medications; including intravenous fluids or blood products. All nine patients were interviewed by the investigators concerning the events of November 3. The nephrologists, nursing personnel, and individual in charge of maintenance of the WTS were also interviewed by investigators.

To determine whether an outbreak had occurred we compared predialysis, intradialysis, and postdialysis blood pressure measurements and heart rates of case-patients during the outbreak and the dialysis sessions immediately following the outbreak. To control for potential factors, a side from contaminated dialysis fluid, that may have contributed to the development of hypotension during treatment, we compared the morning dialysis sessions of the case-patients to their dialysis sessions later in the day. Only the source of the water used to dilute the dialysate concentrate to produce dialysate differed between the two treatment sessions; in the morning session the dialysis fluid was produced from the WTS product water and in the afternoon session tap water was used. The type of dialyzers (same lot numbers), the type of dialysate concentrate, the dialysis stations, and the particular dialysis monitors were the same for both treatment sessions for all 9 patients.

To evaluate whether the case-patients may have been predisposed to developing hypotension or other adverse reactions during their hemodialysis, we conducted a cohort study. We reviewed 1672 consecutive hemodialysis treatments among all patients receiving treatment at the dialysis unit from September 1 through November 1, 1988 (the preoutbreak period) for adverse reactions during dialysis. The dialysis records of the case-patients and non-case-patients were reviewed for signs and symptoms of hypotension, headache, pyrogenic reactions, cramps, nausea and emesis, and other miscellaneous complications (itching, myalgia, chest discomfort).

Laboratory methods

We collected water and dialysate samples to measure bacterial and endotoxin concentrations at several locations along the WTS. Each sample was collected in a sterile, pyrogen-free tube, refrigerated, and sent to the Centers for Disease Control (CDC) for testing. Specimens were cultured and endotoxin levels measured within 48 hours of collection. Viable cell counts in fluid samples were determined with the membrane filtration technique using R2A agar. After the filters (0.45 micron) were incubated for 72 hours at 30°C, colonies were counted. Bacterial endotoxin measurements were determined by the LAL-5000^{Tm} turbidimetric assay system using *Limulus amebocyte* lysate (Pyrotel, Associates of Cape Cod, Cape Cod, Massachusetts, USA).

Water specimens were collected at points along the WTS before and after flushing of the WTS with deionized water on November 3. These samples were tested for total organic carbons (TOC) and sodium azide concentrations by Upstate Laboratories (Syracuse). Serum specimens collected from all nine patients at 0830 hours on November 3 were also tested for sodium azide concentrations.

Total organic carbons were determined from a 1-ml fluid sample with a T.O.C. analyzer (OI Corporation, College Station, Texas, USA). Ion liquid chromatography was used to measure the total sodium azide content in 50 to 100-ul fluid samples.

Statistical analysis

Proportions were compared using the chi-square test. The significance of difference between means was assessed by Fisher's *t*-test.

Results

Epidemiologic investigation

All nine patients who underwent dialysis during the morning session of November 3 met the case definition for outbreak-associated hypotension (Table 1). Eight of nine patients (89%) exhibited symptoms; the patient without symptoms had a decline in systolic blood pressure of 88 mm Hg during her treatment. The frequency of symptoms among case-patients included: headache, six patients (67%); blurry vision, five patients (56%); nausea or emesis, three patients (33%); and syncope, two patients (22%). All patients recovered completely within 5 to 40 minutes after discontinuing dialysis.

Table 1. Clinical characteristics of case-patients in a dialysis unit in New York, November 3, 1988

Patient	Age	Sex	Prior number of CHD treatments	November 3 Time of onset *hours*	Duration	Blood pressure *mm Hg* Pre	Intra[a]	Post	Symptoms
1	65	M	520	0610	20	170/98	50/30	134/80	BV; HA; N/E
2	66	M	405	0613	66	180/90	60/40	128/72	BV; HA; SYNCOPE
3	64	M	570	0630	60	110/80	40/—	138/66	BV; HA; SYNCOPE
4	71	M	751	0630	45	156/80	90/—	167/80	BV; HA; CR
5	67	F	1119	0715	45	180/80	100/60	160/90	BV
6	61	F	1142	0635	90	188/62	100/54	120/80	NONE
7	65	M	1097	0640	40	138/80	70/40	120/60	HA
8	75	M	154	0645	30	140/78	84/40	138/76	N/E
9	52	F	421	0655	20	148/72	64/42	154/78	HA; N/E

Abbreviations are: CHD, chronic hemodialysis; BV, blurred vision; HA, headache; N/E, nausea/emesis; CR, cramps.
[a] Single lowest recorded value

The nine case-patients began their dialysis treatments between 0610 and 0715 hours at dialysis stations located at several points along the distribution loop, which suggested a common source of exposure. The mean values for the lowest single systolic and diastolic blood pressures recorded during dialysis for case-patients differed significantly between their morning and afternoon dialysis sessions on November 3, (73/34 mm Hg vs. 122/62 mm Hg, $P < 0.002$). The mean values for case-patients' pretreatment and posttreatment systolic and diastolic blood pressure measurements and heart rate did not differ significantly between sessions. Only one patient developed hypotension (asymptomatic) during hemodialysis in the later session, (systolic blood pressure dropped from 105 mm Hg to 72 mm Hg at 180 minutes after onset of dialysis). In contrast, case-patients had significantly lower systolic and diastolic blood pressures than did non-case-patients during the outbreak period. No episodes of headache, nausea or emesis, cramps, rigors, fever, or syncope occurred during the later dialysis sessions. These results suggested that an outbreak had occurred and that the water from the WTS appeared to be the source of the outbreak.

Next, we compared the characteristics and signs and symptoms of case-patients and non-case-patients during preoutbreak dialysis sessions (September 1 through November 1, 1988), to determine whether case-patients had risk factors for or were more likely to have adverse reactions during dialysis. During the preoutbreak period, hypotension occurred in 255 (15.2%) episodes of the dialysis treatments. Ninety percent (229) of these episodes occurred more than 60 minutes after the onset of dialysis (median; 180 minutes); 24 (9.4%) occurred between 30 and 60 minutes after the onset of dialysis and two episodes of hypotension (including one cardiac arrest due to arrhythmia) occurred within 30 minutes of the onset of dialysis. The incidence of other adverse outcomes during dialysis were: nausea or emesis; 91 episodes (5.4%); cramps; 67 (4%); headache; 23 (1.4%); miscellaneous symptoms (itching, chest discomfort, myalgia); 23 (0.1%); no pyrogenic reactions were identified.

Among the host factors evaluated for the two patient groups, only the mean number of chronic hemodialysis treatments differed significantly (630 treatments for case-patients vs. 249 for non-case patients, $P = 0.001$). During the preoutbreak period, there was no significant difference in the incidence rate of hypotension during dialysis treatments for the case-patients and non-case-patients. For other adverse reactions, only the incidence of cramping during hemodialysis was significantly associated with case-patients (24 episodes in 238 treatments for case-patients vs. 43/1,434 for noncase patients, $P < 0.001$). These results suggest that no particular host factor among the nine case-patients were associated with the occurrence of hypotension during dialysis treatments.

The incidence of hypotension during dialysis treatments for the case-patients was significantly higher during the outbreak period than during the preoutbreak period (9/9 vs. 27/238, $P < 0.00001$). We compared preoutbreak and outbreak hypotensive episodes of case-patients: 1) onset at <30 minutes after the onset of dialysis (9/9 vs. 0/238); 2) onset >30 minutes and ≤60 minutes after the onset of dialysis (0/9 vs. 0/238); 3) >60 minutes after the onset of dialysis (0/9 vs. 27/238). The difference between the incidences was significantly different for only the episodes of hypotension that occurred within the initial 30 minutes of treatment, ($P < 0.00001$). These data show that the incidence of hypotensive episodes among case-patients was significantly greater during the outbreak period than during the preoutbreak period and that this difference was due to the increased rate of hypotension within 30 minutes of onset of dialysis.

We reviewed the dialysis records of 17 of the 19 patients who received hemodialysis immediately following the previous exchange of ultrafilters on April 17, 1987 but found no signs or symptoms of dialysis associated hypotension. There was no documentation of whether the ultrafilters had been rinsed before they were installed.

Laboratory results

Microbiologic investigation. The highest concentrations of bacteria and endotoxins were found in city water and points early in the WTS (endotoxin concentrations ranged from 8.7 to 62.8 ng/ml, and bacterial counts ranged from 17 to 3300 CFU/ml). The water used to prepare the dialysate and the dialysate specimens collected during treatment were generally within the AAMI maximum recommended microbial concentrations for water used to prepare dialysis fluid (<200 CFU/ml) and for dialysate (<2,000 CFU/ml).

Chemical analysis. Sodium azide was not detected in water samples obtained from the WTS (lower detection limit of 5

Table 2. Chemical results for total organic carbons and sodium azide of water specimens and patient serum specimens, New York, November 3–4, 1988

Sample site and time collected	Total organic carbons	Sodium azide[a]
	mg/liter	
Water specimens from the distribution loop		
November 3, 1000 hours, prior to rinsing of WTS	33	<5
November 3, 2000 hours, after rinsing of WTS	4.7	<5
November 4, 0900 hours, after rinsing of WTS	<1	<5
Patient serum specimens[b]		
November 3, 0830 hours	—	<0.5

[a] By ion liquid chromatography.
[b] Includes all 9 case-patients.

mg/liter; Table 2). However, TOC levels were elevated (normal <1 mg/liter), within the distribution loop at 1000 hours on November 3 and declined to nondetectable levels within 24 hours of rinsing the WTS with deionized water. Sodium azide was not detected in the blood of the nine case-patients obtained at 0830 hours on November 3 (lower detection limit of 50 parts per billion).

Discussion

This cluster of hypotensive episodes among patients appeared to be due to a contaminant in the WTS, probably sodium azide, which resulted in contaminated dialysate. This outbreak underscores the potential for adverse reactions secondary to inadvertent introduction of contaminants into the WTS in a dialysis unit. All nine patients who were undergoing dialysis at the time of the outbreak experienced significant signs or symptoms of hypotension within minutes of the onset of dialysis. Although hypotension among patients receiving hemodialysis during the preoutbreak period was not unusual (15% incidence), episodes of hypotension occurring within 30 minutes of onset of dialysis were very infrequent (<0.1% incidence). In this outbreak, there was a significant increase in the incidence of hypotensive episodes occurring within 30 minutes of the onset of dialysis treatments.

The rapid onset of symptoms, the high attack rate among patients throughout the unit, and the fact that symptoms resolved quickly and completely within minutes of discontinuation of dialysis suggested a common source exposure to a hypotensive agent. Localization of the source to the WTS of the dialysis unit is supported by the observation that all nine case-patients subsequently underwent dialysis without incident later on the same day when only the treatment of the water used to produce dialysis fluid had been changed.

If sodium azide, which is known to cause hypotension in humans, was the contaminant, it probably came from the four unrinsed new ultrafilters put on-line 12 hours before the hypotensive event. Water specimens collected from the distribution loop at the time of the outbreak tested negative for sodium azide but contained high TOC concentrations. The high TOC content could be explained by the presence of glycerine, which was used with azide as a preservative solution for the new ultrafilters. The glycerine concentration within the preservative solution was 100 times that of sodium azide and may explain why an elevated TOC concentration (and not sodium azide concentration) was detected within the WTS.

Sodium azide is a colorless neutral stable salt of hydrazoic acid and was once extensively used as a preservative of serum and other reagents in bacteriologic labs. In vitro studies have shown that it inhibits cytochrome oxidase and other enzymes [11]. The toxicity of sodium azide ingestion or inhalation has been reported in studies of lab personnel, workers involved in lead azide manufacturing, and persons who have committed suicides [11–15]. It is a very potent hypotensive agent, producing vasodilatation via its direct action on smooth muscle. The hypotensive dose of sodium azide in humans is 0.2 to 4.0 μg/kg [15, 16]. Symptoms of dysphoria, headache, nausea, and dimness of vision have also been reported with small doses. Large ingested doses in humans produce convulsions and death. The signs and symptoms observed in the nine case-patients are consistent with the pharmacologic effects of sodium azide; therefore it was the likely contaminate in the dialysis fluid that caused this outbreak.

The manufacturer of the ultrafilters estimates that 0.8 g of sodium azide was contained within a single ultrafilter cartridge. Using an approximate total volume of 1000 gallons within the WTS, a 50% rejection rate of feed water by the RO membranes, and a dialysis fluid flow rate set at 500 ml/min, we determined that a hypotensive dose of sodium azide (300 μg) could be delivered to a 70 kg man within the first five minutes of dialysis treatment.

In 1986, 1350 chronic hemodialysis centers in the United States representing approximately 90,000 dialysis patients were surveyed; only 12 (<1%) of the centers did not indicate use of a WTS [17]. Deionizers with or without reverse osmosis membranes were the most common components within WTS as reported by hemodialysis centers. The Food and Drug Administration (FDA) considers a WTS within a dialysis center to be a medical device when it is intended to remove organic and inorganic substances and microbial contaminants from water used to prepare dialysis fluid [18]. As with other Class II medical devices (such as, blood access devices), a WTS within a dialysis center is subject to performance standards in addition to general controls. Although AAMI has published guidelines for the quality of water used to prepare dialysis fluid, to date the WTS in hemodialysis centers has not been regulated. The task of regulation is made difficult by the large number of dialysis centers, each of which uses a WTS with a unique design. When installing a new WTS or modifying an existing one, the owner/operator of the dialysis center may consult with different manufacturers of WTS or with a qualified water engineer familiar with the special needs of dialysis facilities [10]. In addition, because the dialysis center does not sell the uniquely configured WTS, the owner/operator is not required to register as a medical device manufacturer.

This was the third time during 1988 that adverse reactions occurring in dialysis patients exposed to chemically contaminated dialysis fluid were investigated by officials from FDA and CDC. In all instances, patient morbidity might have been avoided if the dialysis centers had properly rinsed their WTS

after disinfection, maintenance or modification, and if appropriate chemical test kits were used prior to and during resumption of dialysis. We suspect that similar events have occurred but have gone unreported.

Prevention

The cornerstone of prevention of WTS complications in hemodialysis patients is recognizing that water produced by a WTS is a dynamic system subject to changes occurring outside and within the dialysis center, and it therefore requires careful and frequent monitoring of all aspects of the WTS for potential problems. We recommend the following to practitioners as a guideline to prevent chemical contamination within the WTS:

1. Each hemodialysis center must employ an individual qualified in routine maintenance of the WTS. This person must be familiar with the chemicals used for disinfection of their water sources and with the WTS in use.

2. When changes in the WTS are being considered, all components of the system and their interaction should be evaluated before any changes are implemented. After modifications (including replacement of used components), dialysis center personnel need to ensure that the water used to prepare dialysis fluids meets AAMI standards, and is free from toxic chemicals.

3. Ultrafilters should be installed according to the manufacturer's recommendations and care should be taken to rinse each ultrafilter thoroughly before being put on-line within the WTS [19].

4. After a WTS disinfection, water from several point-of-use stations should be tested for residual disinfectant with an appropriate indicator before dialysis treatments are resumed.

5. Because many municipal water treatment facilities routinely add chloramines to the water supply which can be harmful to dialysis patients if allowed to remain in the water used to prepare dialysates, practitioners must be assured that the maximum expected level of chloramines from the municipal water supply can be effectively removed by the WTS [10]. We recommend the use of charcoal filters containing granular activated carbon (GAC) and replace rather than regenerate the filters when exhausted.

6. Finally, clusters of adverse reactions or infections occurring among patients during dialysis should be reported immediately to local and state health departments and to the Office of Compliance, Device Monitoring Branch, Center for Devices & Radiological Health, Food and Drug Administration [Telephone: (301) 427-8144].

Acknowledgments

We thank Dr. Tom Lowe, Mary T. Carden, and Sherry L. Philips of the FDA, and the personnel of the dialysis center for their assistance in the investigation. The authors also thank Carol Snarey for her help with editing the manuscript and Geraldine Jones for her assistance in preparing the manuscript.

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